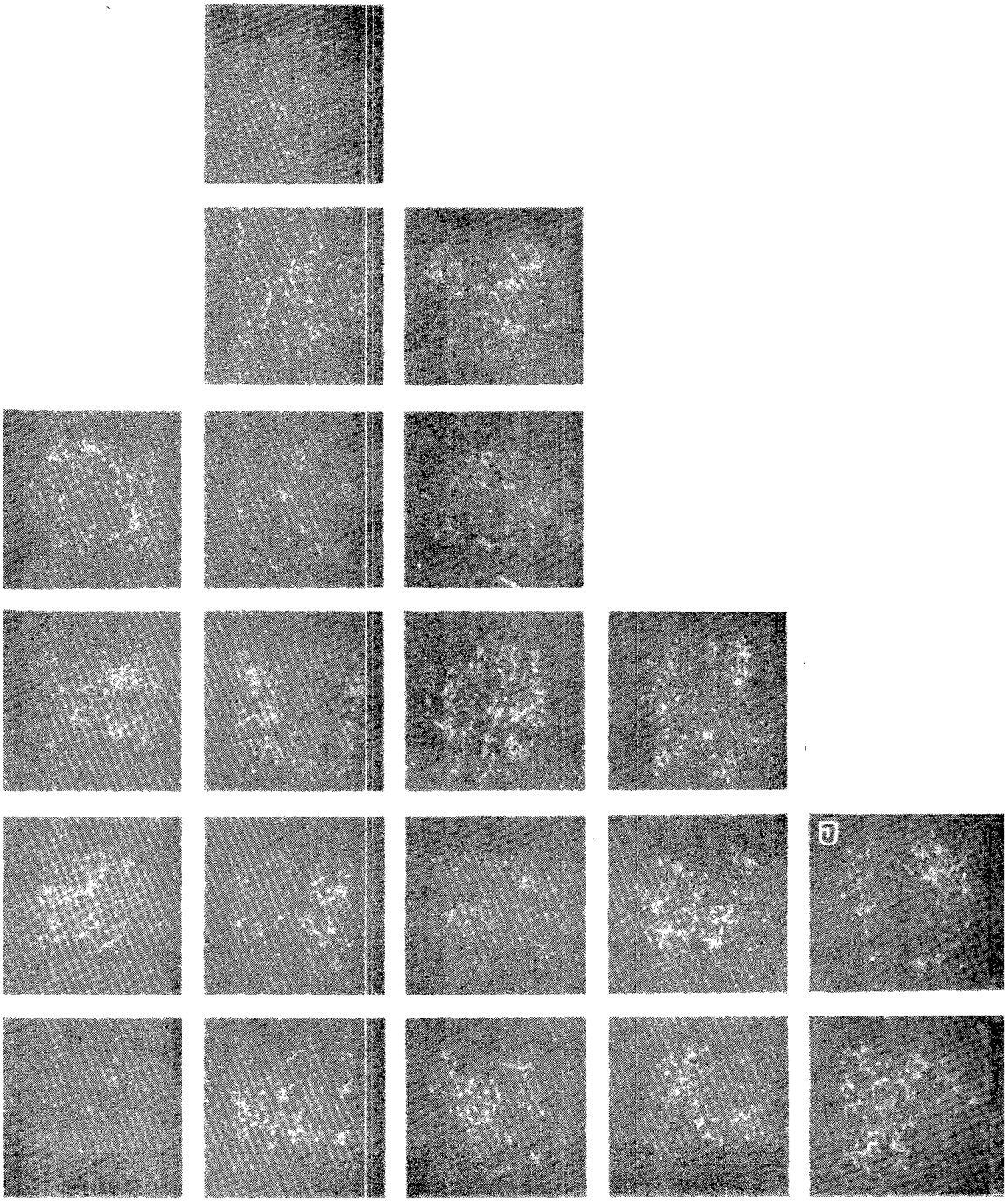
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SOME CURRENT VIEWS ON BRAIN MONOAMINES

(CONTINUED)

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PHYSIOLOGICAL ROLE OF BRAIN MONOAMINES

USE OF DRUGS THAT BLOCK STORAGE IN STUDIES OF BRAIN MONOAMINES

Because of the inaccessibility of specific pathways in the central nervous system, the function of brain amines cannot be ascertained by the same type of simple and convincing experiments that have shown the role of neurohormones in the peripheral nervous system. A conventional approach has been to determine the physiological changes produced by intravenous injection of the substance.

However, it is not easy to translate these effects in terms of a normal role because the exogenous amine is spread throughout the body and may elicit alterations in function quite different from those it would cause if released at its reactive sites. One has only to remember that many studies of injected histamine have not revealed its physiological role. An additional difficulty arises from the poor penetration of monoamines into brain. The large doses needed to evoke a central action also produce peripheral effects.

To circumvent the blood-brain barrier, 5HT is administered in the form of its precursor 5HTP on the assumption that the central effects of the 5HT formed in brain reflect the normall action of endogenous 5HT. In studies with 5HTP the assumption is usually made that 5HT is formed only at sites where this amine is normally made and stored. However, 5HTP and DOPA are decarboxylated by the same enzyme (12,25), and therefore 5HT will also be formed at catecholamine sites. As shown later, the effects of a high level of free 5HT confined to its normal sites of action are quite different from those produced by 5HTP (64).

When studies in our laboratory (65) first demonstrated that reserpine depletes brain 5HT, we explored the possibility that a drug which blocks the storage of an amine might disclose the normal function of this amine. If a drug blocks the storage of only one amine, changes in physiological, psychological, biochemical and EEG behavior might suggest which neuronal pathway is modulated by the substance. When more than one amine is affected it is necessary to find a more selective agent. Reserpine is particularly useful in studying brain amines since it blocks their storage (66) but not their formation (67). Another advantage of reserpine is its nonreversible action. Thus, interpretations are not clouded by effects which result from reversible combinations of drug molecules with cell constituents.

Kinetics of formation, release and disappearance of brain amines after blockade of storage

Since all compounds that block the storage of brain 5HT also produce a characteristic reserpine-like syndrome, it is tempting to attribute the pharmacological effects to this action (65,67,68,69). In attempts to associate (or dissociate) reserpine action with amine changes, it is often assumed that blockade of storage will produce the same physiological effects as blockade of synthesis. Accordingly a depletion of amine stores is usually equated with a deficiency of free amines at reactive sites (70). The amines are formed continuously and newly-formed molecules are either stored, or inactivated by MAO. Levels of amines at active sites depend mainly on release from storage which is under

nervous cntrol. Although reserpine impairs processes that store amines, synthesis continues unabated, and without a mechanism for storage newly-formed molecules flow unobstructed onto reactive sites. The effect of reserpine will now depend on the resultant level of amines at these sites. This in turn is determined by the balance between rates of synthesis and disappearance. Consideration should be given therefore to the kinetics of amine formation, metabolism, and diffusion after blockade of amine storage.

If formation is slow compared to disappearance, the equilibrium level will be too low to produce a persistent response. Presumably this happens at peripheral sympathetic sites where free NE is formed too slowly to maintain sympathetic tone. Contrastingly, if formation is rapid relative to disappearance, then the level at equilibrium will be sufficient to produce apersistent response. In this regard, the enormous activity of the amines in the free form must be appreciated. For example, the uterus of rats which have been given 5HTP shows no contractile activity in Locke's solution, even though the muscle contains 3.8γ/g of 5HT. If 0.01γ/ml is now added, a strong contraction results (64). Thus in the free state the amine is active with only about one part in several hundred. Available assay methods do not yield a conclusive answer of whether reserpine produces a deficiency of NE at reactive sites in the brain. However, assay of heart NE after reserpine administration indicates that the level is virtually zero, while small amounts of NE are detectable in brain (71). Moreover, NE must be present in amounts sufficient to maintain central adrenergic output as evi denced from the electrical recording or preganglionic impulses which shows a greater than normal sympathetic output (72,73).

The possibility that uncontrolled release results in a sustained level of 5HT at reactive sites must now be seriously considered in view of the recent articles of Bulbring and Crema on reserpine action in the guinea pig gut (74,75). These authors have shown that on treatment with enough reserpine to deplete 5HT stores, there is an increased peristaltic activity due to the uncontrolled pelease of 5HT onto sensory receptors which regulate contractibility of the gut. The balance between formation and inactivation of 5HT is such that active sites are continuously occupied by the amine.

Two factors favor the view that reserpine action in brain is caused by an uncontrolled release of 5HT onto reactive sites. First, 5HT is formed extremely rapidly compared to NE (24); second, and perhaps of more consequence, the blood-brain barrier does not permit the ready passage of free 5HT into the blood stream. In contrast there is no hindrance to the diffusion of NE released at peripheral nerve endings.

When this laboratory showed that reserpine inhibits 5HT storage and produces sedation for the same length of time, it was proposed that the two events were causally related (65,66). This view seemed plausible as many effects of reserpine, including tranquilization, decreased motor activity to external stimuli, and increased parasympathetic outflow, are elicited by electrical stimulation of areas in the limbic system (76) and diencephalon (77), where 5HT is heavily concentrated. Reserpine was postulated to stimulate a neuronal network modulated by 5HT which ties in central parasympathetic activities with patterns of behavior for conservation and protection of organisms (1).

When other workers announced that reserpine also blocked NE storage processes (78,79), this seed of a theory for the role of 5HT, based on reserpine action, seemed to have fallen on unfertile soil. In its place sprouted the view that the central effects of reserpine are caused by deficiency of catecholamines at reactive sites. The change in 5HT seemed no longer necessary to explain reserpine action. Carlsson *et al.* (80) fertilized this view by demonstrating that dopamine (from DOPA administration) counteracts the tranquilizing action of reserpine and suggested that the high brain level of dopamine could substitute for the loss of NE. The same argument has been used by Everett and Toman (81) to explain the reversal of reserpine action by desoxyephedrine. The concept that reserpine causes NE deficiency in brain is based on the assumption that the kinetics of amine formation and disappearance are the same in brain as in peripheral neurons; and that dopamine and desoxyephedrine overcome the action of reserpine rather than counteracting its effects through physiological antagonism.

Support for Carlsson's view was soon forthcoming. On the basis of monoamine bioassays with a wide range of experimental variability, Karki and Passonen (82) concluded that raunescine causes sedation in rats at doses that selectively release brain NE. By using precise fluorometric methods, our laboratory found that sedative doses of raunescine causes an equal lowering of the levels of both amines (69). Pletscher *et al.* (58) also proposed that the sedative action of reserpine is associated with loss of NE. The basis for this proposal was data showing that a potent benzoquinolizine (Ro-4-1284) releases more brain NE than a weak congener Ro 4-1398, though the drugs release 5HT to the same extent. However, by measuring the brain amine levels at various times after the drugs, we showed that the more potent compound depletes the most stored 5HT (66).

Despite the lack of direct proof, the very logicality of the catecholamine deficiency theory made it an attractive one. First no clear role for 5HT was evident and its presence in brain as well as its release by reserpine seemed to

be an accidental aberration in nature's orderly arrangements. In contrast the importance of central adrenergic mechanisms in the control of alertness and motor activity was well established (2,4). Moreover, chlorpromazine was considered to cause a functional deficiency of brain NE by antagonizing central adrenergic mechanisms (83) and at first glance evokes a syndrome of effects like that elicited by reserpine. However, the similarity is deceiving; a less superficial comparison soon showed that it is not easy to find two compounds less alike in their central actions. Pharmacological evidence that reserpine action in brain is not caused by catecholamines deficiency.

If reserpine acts through a deficiency of brain NE, then it should affect central adrenergic mechanisms. For example, a substance like chlorpromazine that dampens central adrenergic activity also decreases central sympathetic output. At one time both drugs were thought to depress central sympathetic activity, but Bogdanski *et al.*, in our laboratory demonstrated that the two drugs exert entirely different actions on central autonomic activity (84). These conclusions are based on the demonstration that the effects of reserpine and tetrabenazine on pupillary size, salivation and lacrimation are due to an increased central parasympathetic activity, while the autonomic effects of chlorpromazine are due largely to decreased sympathetic output. Similar conclusions have been expressed by Vogt (85).

The reserpine-induced decrease in sympathetic tone is a peripheral action owing to depletion of NE from peripheral sympathetic neurons (65,78). In contrast, tetrabenazine does not empty the NE stores from peripheral nerves and does not lower sympathetic tone.

Clear-cut evidence that reserpine does not lower sympathetic activity has been provided by studies which show that reserpine does not lower the frequency of nerve impulses along preganglionic sympathetic fibers (70,71). In fact, the frequency of nerve impulses seems to be increased(71). As additional evidence that reserpine can increase sympathetic outflow in rabbit (33) and cat (86) is the centrally mediated stimulation of the adrenal medulla induced by the alkaloid. These results place the primary site of altered sympathetic activity squarely on the peripheral sympathetic system.

The altogether different electrophysiological effects produced by reserpine and chlorpromazine indicate that the drugs elicit sedation by different mechanisms. Chlorpromazine suppresses the effects of sensory stimuli on the reticular activating system, perhaps by blocking the action of NE (87); in contrast, reserpine in doses that prevent storage of brain NE causes a continuous alert pattern, possibly due to uncontrolled release of NE onto reactive sites in the

reticular formation (88,89). Perhaps the most significant difference in the electrophysiological effects of the two drugs is the highly specific action of reserpine in lowering the threshold of excitability of the amygdala to electrical stimulation (90,91). This activation of the limbic system may be an important clue to the mechanism by which reserpine reduces the intensity of emotional behavior.

Perhaps the most decisive difference between the effects of reserpine and chlorpromazine on central adrenergic mechanisms is disclosed by their effects on temperature regulation. Rats pretreated with chlorpromazine cannot regulate their temperature in the cold and after 2 hours at 2°C, body temperature rapidly declines to about 16°C. Chlorpromazine appears to inhibit central adrenergic systems which control mechanisms that conserve and generate heat. In contrast, if rats are given reserpine in doses that completely deplete body NE stores (but not those in the adrenal medulla) and then placed in the cold, the temperature declines only a few degrees over a period of several hours (92).

Physicochemical evidence that reserpine action in brain is not caused by a catecholamine deficiency

Since reserpine, unlike chlorpromazine, does not lower sympathetic output it must be assumed that despite loss of NE stores, the free amine is still present at reactive sites. Can this view be supported on kinetic grounds? First we must remind ourselves that a large number of studies show that reserpine **produces**

Table 2

Pharmacological Effects and Brain Amine Levels after Various Doses of Reserpine in Rabbits

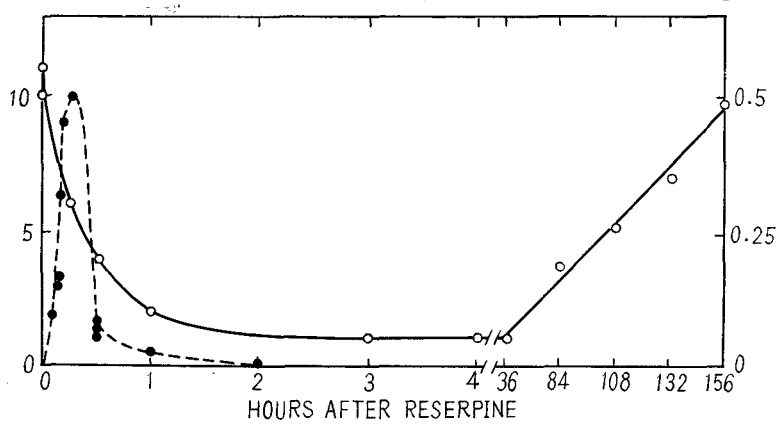
Reserpine mg/kg i.v.	5HT % of controls	NE % of controls	Pharmacological Effects
0.25	60	68	Miosis, enhanced light reflex
0.50	42	53	Above effects+diarrhea, lack of exploratory activity blepharospasm, decreased response to auditory stimuli, decreased resistance to handling
1.00	30	25	Above effects+adynamia
1.50	18	12	Above effects+loss of fighting reflex

pronounced sedation in doses that lower brain NE by only about 55%. Table 2 lists central effects and brain amine levels four hours after administration of various doses of reserpine to rabbits. The results show that profound central effects are induced by doses much smaller than those needed to completely

deplete NE stores. Similarly in mice, as discussed later, a distinct central action is obtained with doses that lower amines by only 55%. This point cannot be stressed too strongly since the hypothesis of NE deficiency implies, as stated by Carlsson (70), that each of the catecholamines may explain the central action of reserpine. On functional grounds it is difficult to conceive of a NE deficiency if 50% of stored amines are still available. For example, lowering of NE stores in peripheral nerve endings to 20% of normal does not decrease sympathetic tone nor the response to nerve stimulation (93).

On relating brain amine levels to sedation it becomes obvious that reserpine action is not caused by a deficiency of NE (Fig.2). If sedation were due only to a decrease in brain NE, then sedation should persist until the brain level of NE returns to 50% of normal. This is not the case. Four hours after a large dose of reserpine (2 mg/kg i.v.) rabbits are heavily sedated and brain stores of

Fig. 2. In ordinates: at left concentrations of reserpine (γ/g); at right γ/g of 5HT and NE in rabbit brain at various times after reserpine (5 mg/kg i.v.). Reserpine broken line and solid circles, monoamines solid line and open circle.



both NE and 5HT have declined to less than 10% of normal (Fig. 2). In 35 hours when the amine levels are still only 20% of normal, the animals are no longer sedated. These results indicate that the central actions of reserpine are not caused by a deficiency of NE or for that matter of 5HT either.

Since the action of reserpine is not related to the loss of stored 5HT or catecholamines, is the action related to the amines in some other way? As discussed previously, since reserpine interferes with storage and not with the formation of monoamines, the decline in brain levels is proportional to the inhibition of storage and consequently a measure of the uncontrolled release of newly-formed amines.

The greater the uncontrolled release, the better the chance that sufficient free amines will reach the reactive sites. On this basis, only when storage of 5HT is

blocked by 50% is there enough uncontrolled release of the amine to stimulate the reactive sites.

Returning to Fig. 2, why do animals recover in 36 hours when the 5HT level in brain is still only 20% of normal? The clue to this question is provided by the changing shape of the curve which suggests that storage processes are recovering, and now can take up enough of the newly-formed amine to lower the amount of free 5HT at active sites. Two pieces of evidence favor this interpretation. First, treatment with reserpine once again depletes brain 5HT and elicits profound sedation; second, preliminary experiments show that storage sites are now able to take up exogenous amine. But irrespective of the actual mechanism of reserpine-induced sedation, it is difficult to explain it on the basis of catecholamine deficiency.

Selective blockade of catecholamine storage

Until the question is settled whether or not reserpine action is mediated through deficiency of NE, it is difficult to carry out constructive investigations on the role of 5HT in brain. Because of the importance of resolving this matter, we have now taken a new approach. *A priori* one event can be proposed as the cause of another only if there is a clear-cut correlation between the two events. Hence, we have tried to establish whether the action of reserpine is correlated to the change in NE or to the change in 5HT. For these studies we now have drugs that differentially block one of the storage processes.

When we learned that the compound α-methyl-m-tyrosine (27,28,29) (hereafter referred to as MMT) releases brain NE without affecting 5HT it seemed to us that studies with this substance might finally decide the question of whether depletion of NE stores causes sedation. The closely related analogue, α-methyl DOPA (26), also releases NE but the action of MMT is more specific since the large doses of α-methyl DOPA needed to deplete NE stores in rabbits and mice, also deplete considerable amounts of 5HT and elicit sedation (94).

To appreciate the physiological implications of the studies with MMT it should be borne in mind that the dopamine and NE content in brain are about equal, dopamine is localized almost completely in the corpus striatum (13,95). Only traces are present in brain stem where it probably functions only as a transient precursor of NE (95). Consequently, those behavioral effects caused by action of reserpine on brain stem or limbic system are unlikely to be associated with changes in dopamine.

The effects of MMT were determined in the brain stem of rabbits and the whole brain of mice. In the rabbit MMT (100 mg/kg) exerts striking action. With only a small transient decline in the 5HT level it produces a depletion of

catecholamine stores which is still complete after 7 days. Despite the loss of catecholamine stores, the animals show none of the central effects associated with reserpine. Table 3 illustrates the high selectivity of MMT in releasing NE in rabbits. Doses as low as 10 mg/kg release brain NE stores almost completely without appreciably affecting those of 5HT. A dose of MMT 40 times this threshold dose lowers brain 5HT by only 35%. Even at the larger doses the animals display no overt sedation.

Table 3
NE and 5HT Stores of Rabbit Brain Stem 13 Hours after Various Doses of MMT

MMT	Loss of 5HT	Loss of NE
mg/kg i.v.		
10	none	75%
25	none	complete*
50	none	complete
100	25%	complete
400	35%	complete

* The fluorescent reading is about 10% of control values, but it is known that much of this is due to tissue blank.

In mice the action of MMT is considerably less prolonged than in rabbits. Administration of the compound (160 mg/kg i.v.) causes only a transient decline in brain 5HT level but depletes brain NE stores almost completely for 24 hours. Within 36 hours however, the levels have risen perceptibly. Dopamine stores

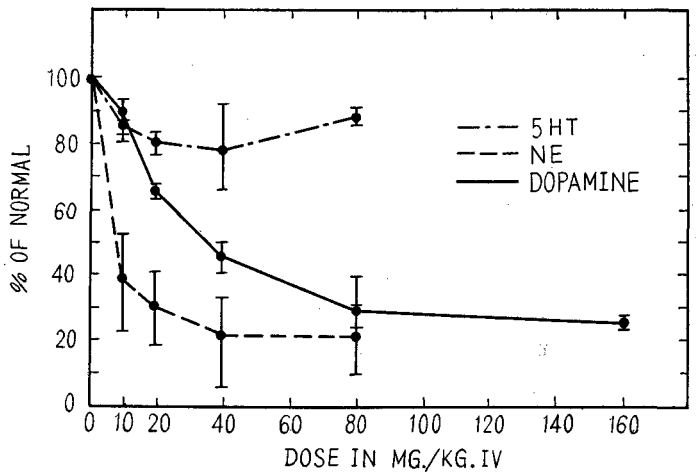
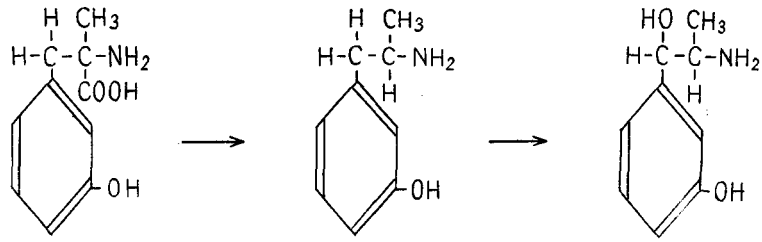


Fig. 3. Levels of amines in mice brains 4 hours after the intravenous administration of various doses of MMT. Vertical bars represent the range of values in 4 experiments. Each point represents the mean of at least 4 experiments. For assay of NE and 5HT content, brains of 6 animals were pooled; for assay of dopamine 14 animals were pooled. Amine control levels (mean of 20 experiments) were : 5HT 0.54 γ/g ; NE 0.47 γ/g; dopamine 0.52 γ/g.

are also depleted but in 10 hours have returned to 50% of normal. Despite the decrease in brain catecholamine stores, the animals show no sedation or other effects associated with reserpine. The effects of various doses of MMT are shown in Fig. 3. After doses of 40 mg/kg the catecholamines are depleted with little effect on 5HT, as little as 20 mg/kg almost completely releases NE and part of the dopamine.

The decline in brain NE induced by MMT does not result from inhibition of catecholamine synthesis but through inhibition of the storage processes (96, 97,98) the action of MMT effect is not a direct one since it does not occur when its decarboxylation is prevented*. The blockade of storage is caused by the small amount of the decarboxylated product, α-methyl-m-tyramine formed in brain. About 30% of this compound is oxidized to the β-hydroxy derivative.



Both products exert relatively little sympathomimetic activity, but are extremely potent in blocking NE storage, the hydroxylated product being 10 times more active than α-methyl-m-tyramine.

Blockade of NE storage has been demonstrated in studies which show that the synthesis of brain catecholamines is unimpaired (98). In addition Hess *et al.* have shown that MMT impairs the uptake of exogenous NE by the heart (98). One is certainly tempted to conclude that if MMT completely depletes brain NE stores without producing sedation, then the sedation induced by reserpine is not due to loss of NE storage. However, a staunch defender against this latter view might hold out with the hypothesis that sedation would have been observed had it not been masked by the action of MMT metabolites (α-MMTyramines). Dr. Carlsson has made the resourceful proposal that the α-MMTyramines formed from MMT replace catecholamines in storage sites and then act like the neurohormones (99). As we interpret this view, the catecholamines are not released by direct inhibition of storage processes, but are displaced by *ersatz* molecular counterparts matched so perfectly that they assume the

* The compound N-(3-hydroxybenzyl)-N-methyl-hydrazine, supplied by courtesy of Dr. E.M. Bavin of the Smith and Nephew Research, Ltd., Ware Herts, England, was used to block MMT decarboxylation. In mice pretreated with the inhibitor threshold doses of MMT fail to release heart catecholamines (97).

functions of NE and dopamine. This idea would explain why depletion of brain catecholamines by MMT does not cause sedation (or excitation).

There are evident difficulties in explaining how the catecholamines stores in rabbit brain stem are empty for more than 7 days after a single dose of MMT, which forms only transient traces of α-MMTyramines. To satisfy the conditions of the replacement theory, the α-MMTyramines must meet the following requirements: 1) Have an extraordinary affinity for storage sites exactly to replace the catecholamines; 2) undergo physiological release by the same process that releases catecholamines ; 3) after physiological release exert a biological activity, exactly that of catecholamines, despite the fact that the foreign amines peripherally exert a biological activity which is extremely low relative to that of NE and 4) in order to explain the depletion of NE in rabbit brain lasting for 7 days, the foreign amines must exert activity without being utilized. In addition, the 2 amines formed from α-methyl-DOPA would also have to meet these exacting requirements. Reconciling these requirements to the rigid demands of kinetics and thermodynamics might be an interesting exercise. Nevertheless, we have tested the validity of the hypothesis solely on quantitative grounds——are the α-MMTyramines formed in brain sufficient to balance the loss of catecholamines? They are definitely not!

We have assayed total α-MMTyramines,using a modified procedure described for m-tyramine* (99). Both amines are stable in the procedure which accurately assays as little as 0.05 microgm/amine/gram of brain tissue.

Table 4 compares the depletion of brain catecholamine stores and the concentration of total α-MMTyramines in rabbits given MMT (100 mg/kg i.v.). In 4 and 7 days, when brain stem catecholamine stores are still depleted, no α-MMTyramines can be detected. These results show a perfect lack of correlation in catecholamine level and the content of α-MMTyramines. Only during the first 2 days do the α-MMTyramines account for an appreciable fraction of the missing catecholamines. The caudate nucleus, the region containing the bulk of the brain dopamine and the highest decarboxylase activity, also contains the largest level of α-MMTyramines. But even here, the amount of α-MMTyramines is less than the loss of dopamine.

Seven days after injection of MMT, the rabbits were given reserpine

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* The amines are extracted from brain homogenate (at pH 10) into butanol. Heptane is added and the total amines are returned to an aqueous phase as described in the 5HT method. The individual amines may be separated, if necessary, by shaking the butanol-heptane phase with buffer pH 9.3 and pH 10. The amines are then coupled with 2,6-dichloroquinonechlorimide to yield colored substances which are extracted into a small volume of butanol and assayed spectrophotometrically.

(2 mg/kg i.v.). The typical reserpine syndrome was evoked including sedation, blepharospasm, enhanced light reflex and increased parasympathetic output without a concurrent change in brain stem levels of catecholamines (already depleted), or of α-MMTyramines (which had already disappeared).

We have also carried out studies in mice, the species used by Dr. Carlsson in his studies of the action of MMT. Table 5 shows the levels of brain catecholamines and total α-MMTyramines in mice given MMT (160 mg/kg i.v.). In 4 hours when NE and dopamine stores in brain are both emptied, total α-MMTyramines account for a considerable fraction, about 60%, of the released catecholamines. However, time-response data shows that in 16 hours NE is still completely depleted and that dopamine is a little more than 50% of normal, but the total α-MMTyramines now amount to only 33% of the missing catecholamines; in 24 hours stores of NE are still depleted but total α-MMTyramines now

Table 5

Comparison between Total α-MM Tyramines (MMTA) Level and Loss of Catecholamines in Brain of Mice given MMT (160 mg/kg i.v.)
Amines calculated as μM/kg

Hours after MMT	Loss of catecholamines			MMTA level (B)	$\frac{B}{A}$
	NE	Dopamine	Total (A)		
	μM/kg	μM/kg	μM/kg	μM/kg	
4	2.4	2.8	5.2	3.2	.61
16	2.4	1.3	3.7	1.2	.32
24	2.4	0.8	3.2	0.7	.22

Each value represents the average of at least 4 experiments.
Brain NE content of controls=2.6 μM/kg; brain dopamine content 2.9 μM/kg.

Table 4

Comparison between Total α-MM Tyramines (MMTA) and Loss of Catecholamines in Brain Stems of Rabbits given MMT (100 mg/kg, i.v.)
Amines calculated as μm/kg

Hours after MMT	A Loss of catecholamine	B MMTA levels	$\frac{B}{A}$
	μM/kg	μM/kg	
48	3.5	1.7	.48
72	3.5	0.8	.23
92	3.5	0.08	.02
168	3.4	0.00	—
192	2.7	0.00	—
288	2.4	0.00	—

Each value represents the average of at least 4 experiments.
Brain stem catecholamines of controls=3. 9 μM/kg.

account for only 20% of the missing catecholamines. Thus, despite the short duration of effect on NE storage in mice, measurements at various periods of time show that total α-MMTyramines account for an appreciable part of the missing catecholamines for a short time and then disappear at a relatively rapid rate.

The argument could be raised that the small amounts of α-MMTyramines formed in brain might, by a direct action, exert a stimulatory effect exactly balancing the hypothetical sedation produced by the loss of catecholamines. According to this view, MMT like DOPA. should counteract the effects of reserpine. In exploring this possibility we found that if reserpine is administered to MMT-pretreated mice, it produces the same characteristic reserpine-like syndrome though the levels of α-MMTyramines are substantially the same in both groups of animals (Table 6). It may be concluded therefore, that amines

Table 6

Effect of Reserpine Pretreatment 5 mg/kg i.v. on Total α-MM Tyramines (MMTA) in Brain of Mice given MMT (160 mg/kg i.v.)

Hours after MMT	Brain MMTA	
	Pretreated with reserpine	Not pretreated with reserpine
	γ/g	γ/g
2	.68	.75
3	.52	.61
5	.23	—
8	.20	.21
18	.12	.14

The intensity of reserpine action is unaltered by MMT injection.

Table 7

Change in Brain Amine Levels produced by Reserpine in Mice pretreated MMT with MMT (160mg/kg i.v) was injected two hours before reserpine (1.5mg/kg i.v.): animals were killed one hour later.

Drugs	Amine levels γ/g				% of mice with reserpine syndrome
	5HT	NE	Dopamine	MMTA	
None	.63	.52	.47	---	0
α-MM	.50	.10	.03	.51	0
α-MMT+Reserpine	.24	.10	.01	.42	78
Reserpine	.26	.17	.04	---	84

Reserpine syndrome was evaluated on a quantal basis. The end points were (1) lack of huddling behavior, (2) lack of exploratory behavior, (3) blepharospasm, (4) hunched back posture, (5) reduction of responsiveness to acoustic stimulation.

formed from MMT do not produce significant central stimulation. These results also show that unimpaired NE storage sites are not needed to account for the presence of α-MMTyramines in brain.

Perhaps the most conclusive experiments are those showing that reserpine administered to MMT-treated mice, can produce sedation with no change in levels of NE, dopamine or α-MMTyramines. In these studies reserpine was given to mice treated 2 hours earlier with MMT to deplete brain catecholamine stores. The mice display the same degree of sedation as animals given reserpine alone although reserpine does not alter the level of any of the amines except 5HT (Table 7).

QUANTITATIVE RELATIONSHIP BETWEEN CENTRAL ACTIONS OF RESERPINE AND BLOCKADE OF 5HT STORES

Experiments with MMT provide additional clear-cut evidence that depletion of catecholamine stores does not produce sedation or other signs of reserpine action. We must now look for some other reason for the sedation and other signs of central reserpine action. Blockade of 5HT storage has not been seriously considered as the cause of reserpine action because of the failure to find a normal role for the amine. This might be putting the cart before the horse for if the central action of reserpine were in fact associated with the change in brain 5HT then studies of reserpine action might disclose the role of this amine. Before accepting or rejecting the feasibility of this view, let us see whether or not the two events——blockade of 5HT storage and the central action of reserpine——show a correlation.

A number of previous studies which need not be discussed in detail have described a qualitative relationship between reserpine action and blockade of 5HT stores. For example, cold-exposure prevents reserpine from inducing sedation and a decline in brain 5HT without affecting the decline in brain NE (101,68,96). Again, SU 5171, the dimethylaminobenzoyl ester of methyl reserpate almost completely deplete NE stores in doses that do not elicit sedation or appreciably lower 5HT(69). In addition experiments with tetrabenazine describe conditions under which NE is almost completely depleted without producing sedation (102). A number of times Dr. Kety has suggested to us that our notions on the role of 5HT have a certain heuristic value but suffer from the fact that they are presented with accurate analytical data but only indefinite criteria of central action (103). We have taken this criticism to heart and have carried out studies in which the central action of reserpine was quantitatively measured.

The availability of MMT provides a means of making quantitative relation-

ships. In these experiments mice are pretreated with MMT to eliminate NE stores from the picture. After 13 hours the animals are given various doses of reserpine and changes in brain 5HT are related to the degree of central activity. This activity is determined by 5 criteria: 1) almost complete immobility and lack of exploratory activity; 2) lack of huddling behavior; 3) blepharospasm; 4) hunch-back posture; and 5) almost no response to acoustic and tactile stimuli. The problem of measuring these criteria is simplified by quantal analysis of the data: each dose of drug is given to a large number of mice and the change in brain 5HT related to the central activity expressed as the number of animals that display all 5 signs. The data in Table 8 shows a close relationship between the degree of central activity and the lowering of brain 5HT and

Table 8

Effects of Various Doses of Reserpine, on Brain Amine Levels and in causing Reserpine Syndrome in MMT pretreated Mice

Dose of reserpine	Brain 5HT		Brain NE		Reserpine syndrome (% of mice)	
	MMT pre-treatment	No pre-treatment	MMT pre-treatment	No pre-treatment	MMT pre-treatment	No pre-treatment
mg/kg i.p.	γ/g	γ/g	γ/g	γ/g		
0	.59	.63	.09	.52	0	0
.6	.43	.43	.05	.24	28	30
1.25	.32	.32	.07	.17	47	50
2.50	.24	.27	.07	.13	76	75
5.00	.18	.19	.05	.11	96	98

Animals were given MMT 500 mg/kg i.p. and 13 hours later the animals received various doses of reserpine. The central effects were noted after 90 minutes and the animals then killed. Control animals were given reserpine without pretreatment with MMT. Reserpine syndrome evaluated as explained in text. Each dose was given to at least 30 mice.

indicate that the degree of reserpine sedation is closely related to the impairment of 5HT storage. The same results are obtained in normal animals and animals pretreated with MMT (Table 8) indicating that MMT does not affect the responses to reserpine.

Additional quantitative data relationships between the degree of central activity and impairment of 5HT storage was also obtained using three different reserpine-like drugs: reserpine itself, which acts nonreversibly and exerts effects persisting long after the drug disappears from the body (52): SU 9064, the methyl ether of methyl reserpate which exerts effects that are dependent on its tissue concentration (57): and RO 4-1284, a synthetic short acting benzoquinolizine, which also appears to be reversibly-acting (58). The results in Table 9

shows the doses of the drug that produce all 5 central signs of reserpine activity in 50% of the animals. For each drug this dose lowered 5HT stores by 55%. These results show that despite different structures and durations of action the central activity of the three drugs is closely related to the impairment of brain 5HT stores.

Table 9

Doses (ED_{50}) of Various Drugs producing in Mice Reserpine Syndrome and reducing 5HT Storage by 55%

	ED_{50}	
	5HT Release	Syndrome of Effects
	mg/kg	mg/kg
Reserpine	.42 (.45-.39)	.43 (.58-.32)
SU 9064	5.8 (9.3-3.6)	8.0 (9.4-6.8)
RO 4-1284	2.6 (4.4-1.5)	4.2 (5.7-3.1)

Animals killed 90 minutes after reserpine and SU 9064 and 25 minutes after RO 4-1284. Central action evaluated on quantal basis from number of animals at each dose that showed all 5 criteria (see text). Effects on brain 5HT storage calculated from number of animals showing the same decline (55%) of brain 5HT. Values in parenthesis represents fiducial limits (P=.001).

Time-course responses also indicate that reserpine action is related to the impairment of 5HT storage. In rabbits, for example, a single dose of reserpine (2 mg/kg) produces depression which lasts for about 30 hours. At this time the capacity of tissues to store 5HT is partly restored and the amine levels have started to rise toward the normal value (66,67).

In cats, the depression produced by a single dose of reserpine(3 mg/kg)lasts over 10 days. Again the recovery of the animals coincides with the recovery of 5HT storage sites and a gradual rise in the 5HT level (102). In contrast, the sedation induced by a dose of Ro 4-1284 lasts only a few hours. Again the recovery of the animals coincides with recovery of 5HT storage (105).

The studies cited above indicate that the central action elicited by reserpine and reserpine-like compounds is closely correlated with the impairment of 5HT storage in brain. Although it is appropriate to point out that an association between two events, sedation and blockade of 5HT storage, merely shows that a causal relationship is possible, nevertheless, the demonstration of this correlation removes a psychological barrier to exploring the feasibility that studies with reserpine might disclose important clues to the role of 5HT in brain.

A lifetime could be spent trying to surmount every possible argument against

the view that reserpine does not act through a NE deficiency. It seems more rewarding and certainly less discouraging to approach the problem in a positive way by trying to link the uncontrolled release of 5HT with the psychological, physiological, electrophysiological and biochemical changes elicited by reserpine.

OPPOSITE ACTIONS OF NE AND 5HT ON ACTIVE SITES

A number of writers have presented the concept that primitive patterns of behavior are controlled by neuronal networks exerting opposite effects and that these systems integrate autonomic function with primitive patterns of behavior. According to this concept, one system (ergotropic predominance-Hess) promotes expenditure of energy by integrating patterns of behavior which prepare the body for positive action (77). Increasing the activity of this system elicits arousal, increases central sympathetic output, mobilizes substrates for energy utilization, increases motor activity and results in exaggerated responses to environmental change. We have postulated that this system might be modulated by NE (5). The other system, normally recessive, integrates behavioral patterns which are recuperative in nature. This system is presumably predominant in sleep and hibernation. Increasing the activity of this system (trophotropic predominance-Hess) elicits drowsiness and sleep, increases central parasympathetic output, decreases motor activity and lowers responsiveness to external stimuli. 5HT has been suggested as the modulator for this system (1). To function in this way, the two amines at their sites of action, should exert effects of an opposite nature.

Effects of Brain Amines Selectively Released after MAO Blockade:

a) Selective Release of NE after MAO Blockade:

If MAO is blocked and NE is selectively released, the amine, highly polar, will be relatively immune from enzymic inactivation and will be trapped in the brain by the blood-brain barrier. The high concentration of the amine at its active sites should now exaggerate the physiological function of the catecholamine.

Mice were treated with the MAO inhibitor MO-911 and 12 hours later brain catecholamine were released by the administration of MMT (30 mg/kg i.v.). The high level of NE available to receptor sites (Fig. 4) results in a remarkable effect on the mice. They behave as though they had been given a super-active amphetamine-like drug. Apparently well-coordinated, they dart at high speed from one side of the cage to the other for a period of 2 hours or more. The relative degree of motor activity in individual animals was measured by taking

20 camera shots per minute on a single film and counting the images in the picture. The hypermobility was found to be at least 10 times greater than that elicited by 5 mg/kg of d-amphetamine. The animals also show other effects associated with stimulation of adrenergic centers including extreme exophthalmos, hyperthermia and an exquisite sensitivity to noise or touch.

These results suggest that the free NE has raised the tone of neuronal pathways associated with central adrenergic mechanisms.

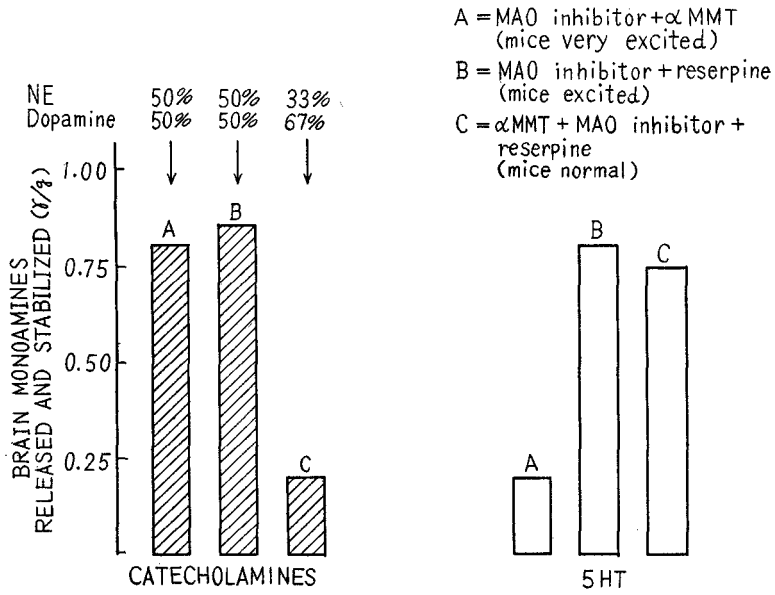


Fig. 4. 5HT and catecholamines (NE+dopamine) released and stabilized by various manipulations as described in detail in the text.

To remove the possible objection that α-MMTyramines or any other metabolites of MMT might participate in producing the excitation, the mice were first treated with MMT (500 mg/kg i.p.) to deplete brain NE stores and 18 hours later given the combination of MO-911 and MMT. No excitation occurs despite the presence of the same amount of α-MMTyramines as in the excited animals which had not been pretreated with MMT. These results indicate that the remarkable behavioral effects induced by MAO inhibitor and MMT results from free NE.

b) Release of both NE and 5HT after MAO blockade:

Both amines are released by treating mice with the MAO inhibitor followed by reserpine. Since the amines were protected against inactivation they are available in high concentration at their active sites. The well-known increased motor activity elicited by this drug combination occurs, but its intensity is about

one-tenth of that evoked by the MAO inhibitor and MMT, as measured by the above-mentioned camera technique. These results suggest that hyperexcitability elicited by free NE is counteracted in part by the action of free 5HT (Fig. 4).

c) Selective Release of 5HT after MAO blockade:

Mice were first treated with MMT to deplete the brain NE stores. After 13 hours the animals were treated with the MAO inhibitor followed by reserpine. As shown in Fig. 4, the free 5HT is immune to enzymic inactivation. The animals are not excited; some are even slightly sedated for a short time, though obviously less so than animals given reserpine alone. These results indicate that a high level of free 5HT, selectively released from its normal sites of formation, does not provoke excitation.

The physiological effects of selectively released monoamines at their sites of action have furnished presumptive evidence that NE and 5HT have different physiological functions. First, free NE produces an intense exaggeration of a syndrome superficially similar to that elicited by DOPA and amphetamine and reminiscent of that described by Hess for a highly activated ergotropic tone. Free NE and 5HT together elicit a much less intense excitation. It is tempting to consider that these results might reflect an action of the two amines on opposing systems. A crucial demonstration of whether NE and 5HT act in opposite ways might be the production of profound sedation by the selective release of 5HT. Unfortunately, it has not been possible thus far to trap only free 5HT in brain. In experiment c, the blockade of MAO also causes accumulation of some free dopamine and NE (Fig. 4). However, the results do show that free 5HT, released from its normal storage site, does not as often suggested, produce excitation.

A SPECULATIVE SUMMARY

An understanding of the role of brain NE and 5HT is particularly difficult since we do not know whether to attribute a transmitter role to the amines or to regard them as substances which modulate the action of the actual transmitters.

The presence of NE in peripheral sympathetic ganglia enabled us to study its interplay with acetylcholine in synaptic transmission by comparing the postganglionic evoked potentials before and after producing a deficiency of free NE in ganglia by means of reserpine or bretylium. A striking indication was obtained that acetylcholine acts on ganglionic chromaffin tissue to release NE. The

liberated amine appears to modulate transmission perhaps by hyperpolarization of the postsynaptic membrane, or by depression of acetylcholine release to dampen the action of acetylcholine and buffer wide fluctuations in sympathetic activity.

Monoamines might also serve as modulators of synaptic transmission in brain. For instance, there is evidence that NE is not a transmitting agent of the reticular activating system, but may modulate the actual transmitter when it is released from afferent collaterals. Chlorpromazine in turn probably blocks this activating effect of NE on the reticular activating system.

Similarly Revzin *et al.* (105) have suggested that 5HT modulates the action of acetylcholine in the limbic system, a brain region containing large amounts of 5HT and little NE. These workers have shown that the degree to which 5HT storage is blocked in that the amygdala system is closely related to behavioral changes and to increased excitability of the limbic system. A single large dose of reserpine depletes stores of 5HT in the cat for 10 days or more and produces sedation that lasts for the same period of time as the alteration in limbic system excitability. In contrast, the benzoquinolizine Ro 4-1284 blocks 5HT storage for a few hours only and causes sedation and limbic system excitation that are correspondingly short-lasting.

The action of reserpine is the first bioelectric phenomenon in brain that is associated with changes in brain 5HT. It is particularly pertinent that the limbic system is not affected by MMT which completely depletes stores of brain catecholamines. However, on treatment of the MMT-pretreated animals with Ro 4-1284 or reserpine, the usual effect on behavior and on the limbic system is obtained.

These results are a background for McLean's (106) observations that the direct application of carbachol to the hippocampus of cat evokes electrical seizures and physiological effects which correspond to those produced by reserpine: sedation, lack of spontaneous movement, disinterest in various stimuli, and a rage-like response to painful stimuli. McLean postulates that carbachol excites hippocampal pathways by mimicking the action of acetylcholine. The results of Revzin *et al.* suggest that 5HT modulates the action of acetylcholine on the limbic system. These workers postulate that this action of reserpine may be largely responsible for lowering the intensity of emotional responses.

One is struck by the common theme of conservation and restoration in the processes set in motion by the action of reserpine-like drugs. (Tetrabenazine is actually a better prototype since it does not lower sympathetic tone by depleting NE stores at peripheral nerve endings). Reserpine produces a sleep-

like state, in some respects similar to that of natural sleep, with active closure of the eyelids and an increased parasympathetic output. The action does not involve suppression of incoming stimuli, but seems to be an active process superimposed on normal function. The drug reduces the heart rate thereby economizing its energy and protecting it from damage in addition there is a conservation of energy from lowered respiration. Additional saving of energy is achieved by the lowering of muscle tone, spontaneous movements and reactions to stimuli. Even such effects as lacrimal secretion and salivation are protective in nature and the increased intestinal activity is also part of restorative processes.

Chlorpromazine elicits somewhat similar effects, but in a far different way. This drug does not actively promote restorative processes, but shuts down functions which are coupled with energy expenditure. Thus arousal reactions and increased motor activity is inhibited by disjunction of the usual connections between incoming stimuli and reticular activating system. Aa a result energy-utilizing processes elicited by sympathetic activity are lowered by a central action.

The difference in the action of the two compounds is dramatically shown by effects on energy utilization. In this laboratory we have compared the action of the two drugs in rats exposed to a low temperature. At 2°C, chlorpromazine completely shuts down both processes that conserve heat and that mobilize energy substrates which are needed to maintain a temperature gradient of 40°C. As a result, body temperature rapidly plummets to 16°C and the animals die. This is due to the blocking of central adrenergic mechanisms since the same results are elicited by ganglionic blocking agents and by removal of catecholamines from the adrenal gland and from the peripheral nerve endings. Indeed we have shown that free fatty acids can be mobilized from adipose tissue only through a centrally mediated sympathetic stimulation.

Tetrabenazine, or reserpine in doses that do not deplete medullary catecholamines, elicit a quite different effect. Exposure of rats to 2°C also elicits a drop in temperature but this is slow, about 10°C over a period of 7 hours. The mobilization of energy substrates is not inhibited, instead the utilization of energy by body tissues is drastically decreased. In some way thyroid action is blocked but not by a direct action on the gland but by events occurring in the tissues.

These results give food for thought since they indicate that chlorpromazine acts on central mechanisms that are oriented towards patterns of behavior which utilize oxidative metabolism and require energy; while in contrast reserpine stimulates pathways which provide for protection and promote restorative processes.

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高橋良，高橋康夫両氏米国に留学

本懇話会の設立以来，常任委員として御尽力下さつていた，高橋良（東京医歯大）と高橋康夫（新潟大）の両氏は最近米国に留学された．両氏の健康と研究の発展をお祈りする．

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